

## RECOMMENDATIONS AND GUIDELINES

# A new hemophilia carrier nomenclature to define hemophilia in women and girls: Communication from the SSC of the ISTH

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### Abstract

Hemophilia A and B predominantly attracts clinical attention in males due to X-linked inheritance, introducing a bias toward female carriers to be asymptomatic. This common misconception is contradicted by an increasing body of evidence with consistent reporting on an increased bleeding tendency in hemophilia carriers (HCs), including those with normal factor VIII/IX (FVIII/IX) levels. The term HC can hamper diagnosis, clinical care, and research. Therefore, a new nomenclature has been defined based on an open iterative process involving hemophilia experts, patients, and the International Society on Thrombosis and Haemostasis (ISTH) community. The resulting nomenclature accounts for personal bleeding history and baseline plasma FVIII/IX level. It distinguishes five clinically relevant HC categories: women/girls with mild, moderate, or severe hemophilia (FVIII/IX >0.05 and <0.40 IU/ml, 0.01–0.05 IU/ml, and <0.01 IU/

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ml, respectively), symptomatic and asymptomatic HC (FVIII/IX  $\geq 0.40$  IU/ml with and without a bleeding phenotype, respectively). This new nomenclature is aimed at improving diagnosis and management and applying uniform terminologies for clinical research.

#### KEYWORDS

bleeding, hemophilia, phenotype, women's health

## 1 | BACKGROUND AND RATIONALE

Hemophilia A and B predominantly direct clinical attention to males due to X-linked inheritance. This common knowledge introduces a bias toward female carriers being asymptomatic. Due to lyonization, a random interindividual X-linked inactivation process, median plasma factor VIII/IX (FVIII/IX) levels of hemophilia carriers (HCs) are 0.60 IU/ml (range 0.05–2.19), and 28% have factor levels  $< 0.40$  IU/ml, which would be defined as hemophilia according to the World Federation of Hemophilia (WFH).<sup>1,2</sup> The common misconception by patients and health-care providers (HCPs) that all HCs are asymptomatic is shifting, due to an increasing body of evidence that contradicts this assumption.<sup>3–7</sup> The term HC, and its associated connotations, such as obligate and possible carriers, has hampered diagnosis, management, and research.<sup>8,9</sup>

For each man with hemophilia, 1.6 female carriers can be identified.<sup>10,11</sup> In the US surveillance database, Centers for Disease Control and Prevention (CDC) Community Counts, only 0.5% of severe, 1.4% of moderate, and ~20% of mild cases are female.<sup>12</sup> In countries with lower health-care resources, where not every male patient with hemophilia may be identified, it is likely that many more women with hemophilia remain undiagnosed.

In most instances, as in men, hemophilia in women is due to an inherited variant on a single X chromosome. Variability in factor levels among HCs is poorly understood and more research is needed to find out whether there is a relationship between the type of gene mutation and plasma FVIII/IX level in HCs.<sup>13</sup> Rarely, a woman may inherit an affected X chromosome from both parents, leading to full expression of the hemophilia variant's severity, or exhibit moderate/severe hemophilia due to an extremely skewed X chromosome inactivation pattern.<sup>14,15</sup> In addition, approximately one in four HCs with normal FVIII/IX levels  $> 0.50$  IU/ml have an increased bleeding tendency.<sup>16–18</sup> In hemophilia A carriers this may in part be due to an impaired FVIII response to hemostatic stress.<sup>19,20</sup> The increased bleeding tendency in HCs typically manifests as excessive mucocutaneous bleeding; bleeding after dental work, surgery, or childbirth; as well as joint bleeds with impaired joint health and consequent poor quality of life.<sup>6,10,21–23</sup>

Hemophilia carriers may not receive care in hemophilia treatment/comprehensive care centers (HTC/CCCs) and thus are likely underrepresented in surveillance databases, limiting our ability to characterize their bleeding symptoms and diagnostic journey.<sup>8,9,24</sup>

### Essentials

- The term “hemophilia carrier” (HC) understates bleeding symptoms in women/girls.
- A new HC nomenclature was defined by hemophilia experts consulting with patient advocacy groups.
- Five new HC categories are: severe/moderate/mild hemophilia, symptomatic and asymptomatic HC.
- Clear, precise nomenclature will enhance diagnosis, management, and research on HCs.

Lack of timely diagnosis and appropriate nomenclature can lead to marginalization of HCs and a poor relationship with the HCPs and payers.<sup>12</sup> Terminologies that acknowledge differences in clinical HC types could contribute to reverse such inadequate and inequitable management. Currently there is no formal classification to apply to hemophilia A and B carriers regarding the FVIII/IX levels. Women and girls with hemophilia are often excluded from clinical trials causing a wide scientific gender knowledge gap, which is skewed toward men with severe hemophilia. As a result, little is understood about the safety and efficacy and pharmacokinetics of hemophilia therapies in women. A more inclusive classification system regarding women and girls is urgently needed in hemophilia to enhance awareness, and improve clinical diagnosis, care, education, and research.

With this shifting perspective, the singular term HC needs to be updated. The aim of this collaborative Scientific and Standardization Committee (SSC) project is to redefine HCs with a new nomenclature, which includes clinically relevant subtypes that better reflect the different clinical and biological categories.

## 2 | METHODS

This collaborative SSC project started in 2017. Based on literature and expert consensus we sought new terminology and a conceptual framework for categorization of hemophilia A and B carriers using an open, qualitative approach, accounting for personal bleeding history, genetics, and baseline factor level, with the goal of improving communication among HCPs, researchers, payers, and bleeding disorders

community members. We aimed to ensure that the term hemophilia would not be universally utilized for HCs, as the term leads to confusion in making treatment decisions about appropriate hemostatic therapies. After significant discussion with hemophilia experts internationally, and review with national hemophilia organizations and local patient advocacy groups to elicit opinions and acceptance, a new nomenclature was drafted that defines women and girls with mild, moderate, and severe hemophilia, according to decreased FVIII/IX levels. Two additional categories: “symptomatic carrier” or “asymptomatic carrier” were proposed to acknowledge that some HCs, despite normal levels, may have an increased bleeding tendency and to avoid utilizing one terminology to characterize all HCs.

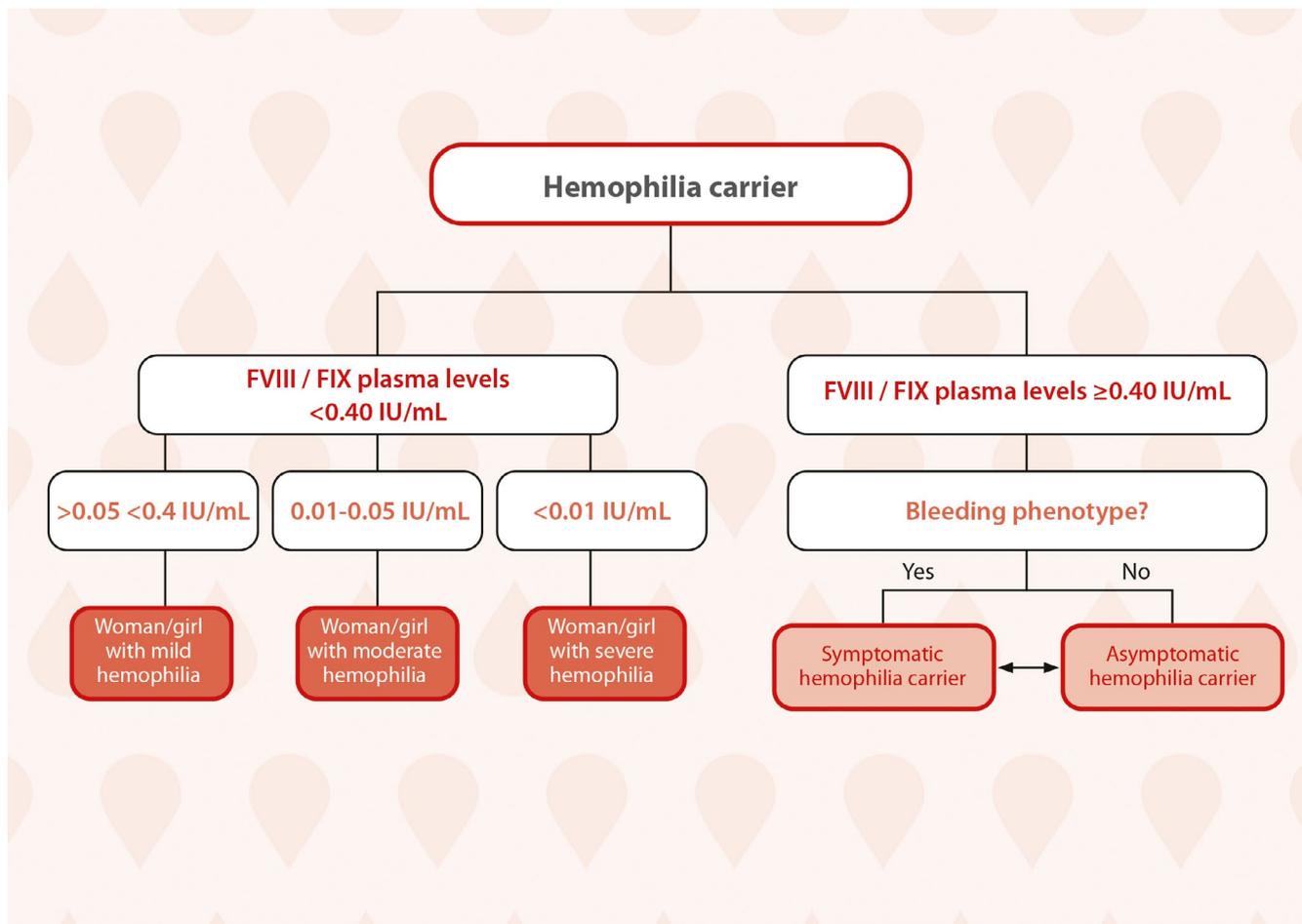
The proposed new nomenclature was presented at the meetings of the SSCs on FVIII/IX & Rare Coagulation Disorder and Women’s Health Issues in Thrombosis and Hemostasis (T&H) during the well-attended ISTH congress July 2019 in Melbourne. Following discussion, a small amendment of the categories for women and girls with mild hemophilia was made to match the WFH criteria for mild hemophilia in males (FVIII/IX <0.40 IU/ml). After no further comments were received, all SSC members present approved the new HC nomenclature.

### 3 | RESULTS

A HC with normal factor levels, as defined by international standards FVIII/IX >0.40 IU/ml, may still have abnormal bleeding. The new SSC-approved nomenclature distinguishes five HC clinical categories (Figure 1). Because bleeding tendency may change during the lifetime of women and girls, a bidirectional arrow was added in the figure to allow for changes in clinical phenotype over time. We suggest that the term HC is reserved for use in discussions regarding genetic counseling and “symptomatic carrier” or “hemophilia” when the focus of the interaction is in response to bleeding concerns.<sup>25</sup>

### 4 | DISCUSSION

Development and standardization of nomenclature is one of the ISTH SSCs mandates. With this joint SSC project, a new nomenclature for HCs was defined based on consensus from experts, consultation of patient advocacy groups, and members of both the ISTH FVIII/IX & Rare Coagulation Disorder and Women’s Health Issues in T&H SSCs. The new nomenclature accounts for personal bleeding



**FIGURE 1** New nomenclature for hemophilia carriers and women and girls with hemophilia. The term “asymptomatic hemophilia carrier” solely reflects the bleeding phenotype, not the actual burden of being a hemophilia carrier. FVIII/FIX, factor VIII/IX; IU/ml, international units per milliliter

history, baseline FVIII/IX level, and distinguishes five clinically relevant HC categories to improve communication, harmonize clinical research, and allow adequate hemostatic management.

Strengths of this new nomenclature are the open, diligent, and iterative process for defining subtypes that match distinguishable categories; incorporation of patient consultations; and alignment of categories with hemophilia males. Potential weaknesses are lack of a validated methodology to reach consensus, the considerable number of defined subtypes, and incorporation of a relatively subjective parameter "bleeding phenotype." It was deliberately chosen for HCs with factor levels  $>0.05$  and  $<0.40$  IU/ml,  $0.01$ – $0.05$  IU/ml, and  $<0.01$  IU/ml to be referred to as a "woman/girl with mild, moderate, or severe hemophilia," respectively. This is to ensure that adequate hemostatic treatment and multidisciplinary management are offered, at least to the same extent as for affected males with hemophilia.<sup>2,26</sup> The abbreviation WGH (women/girl with hemophilia) can be used, although the commonly used abbreviation PWH (people with hemophilia) has the advantage to be gender neutral and is appropriate to include WGH as well. PWH are diagnosed as having hemophilia regardless of bleeding scores. From a psychological point of view the term "asymptomatic HC" might insufficiently acknowledge the true burden of being a HC, and it should be clear that this reflects the bleeding phenotype, not the actual burden. To make sure that any unmet needs are adequately covered, evaluation in real life practice is needed and more data may lead to future nomenclature updates.

Bleeding tendency is most often characterized using the ISTH Bleeding Assessment Tool, which can be accessed online for HCPs and patient self-assessment.<sup>6,27</sup> The scoring system utilizes different cut-off levels to define a bleeding tendency for children, males, and females: respectively,  $>2$ ,  $>3$ , and  $>5$ . Heavy menstrual bleeding (HMB) after menarche is common and as a sole bleeding symptom not necessarily specific for HCs. For adolescents with HMB a bleeding score (BS)  $>4$  is highly specific in predicting a bleeding disorder.<sup>28</sup> Furthermore, prior to defining a HC as "symptomatic," other coagulopathies should be ruled out first when a profound bleeding tendency emerges despite normal factor levels.<sup>29</sup> In addition, we suggest interpretation and classification of "symptomatic HCs" in the clinical context by experienced HCPs in HTC/CCCs, rather than using stringent BS criteria. BS assessment is still important in clinical practice and research, and we do encourage its use and registration in clinical records/registries.

This new HC nomenclature paves the way for future improvements in delivering equitable care, irrespective of gender, with the aim that women and girls will be equally part of the comprehensive care model of hemophilia. It also allows standardized inclusion of relevant HC categories in (inter)national registries, which we strongly encourage, to enhance clinical research and address the current knowledge gaps. Surveillance on better registration could for example start with prospective follow-up of CDC Community Counts on WGH after implementation of this new nomenclature. International consensus is still needed on specific outcome measures that capture gender-specific parameters, which could be defined in a future collaborative project. Furthermore, international collaboration to set standards of care for HCs could be a powerful means to improve

patient care.<sup>30,31</sup> Wide acceptance and implementation of this new nomenclature requires education and clear communication among HTC/CCC, HCPs, international societies, and patient organizations.

## 5 | CONCLUSION

A new nomenclature for HCs has been defined that distinguishes five relevant clinical categories for international standardization of terminology and categorization of this patient group. The new nomenclature better fulfils the needs of this population in receiving medical care and participation in clinical research.

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## CONFLICTS OF INTEREST

Dr. van Galen has received research support from CSL Behring, Bayer, and Octapharma and speakers' fees from Takeda, CSL Behring, and Bayer. Dr. d'Oiron has served as a consultant for Baxalta/Shire, Bayer, CSL Behring, LFB, NovoNordisk, Octapharma, Pfizer, Roche, and Sobi, Spark and was invited speaker for Baxalta/Shire, Bayer, CSL Behring, LFB, NovoNordisk, Octapharma, Pfizer, Roche, and Sobi, Spark. Dr. Sidonio has participated in advisory boards for Novo Nordisk, Sanofi, Genentech, Octapharma, Takeda, Bayer, Sigilon, Catalyst, Biomarin, and Pfizer. Dr. James has received research funding from Bayer. Dr. Mahlangu received research grants from BioMarin, Catalyst Biosciences, CSL, Freeline Therapeutics, Novo Nordisk, Novartis, Pfizer, Sanofi, Roche, Spark, Takeda, and was an advisory board/consultant for CSL Behring, Catalyst Biosciences, Freeline Therapeutics, Novo Nordisk, Roche, Sanofi, Spark, Takeda. Dr. Kulkarni has served on the advisory boards of Sanofi-Genzyme, NovoNordisk, Genentech, CSL Behring, Octapharma, Pfizer, Shire/Takeda, Catalyst Bioscience, and Bayer. Prof Peyvandi has received speaker fees for participating in educational symposia and advisory boards for Roche, Sanofi, Sobi, and Takeda. D. Rotellini has served on advisory boards for Bayer, BioMarin, and Pfizer with National Hemophilia Foundation receiving all honorarium. Prof Abdul-Kadir received lecture fees/educational grants from Pfizer, NovoNordisk, Takeda, and ViforParma. Dr. Sidonio

has IIS funded by Takeda, Genentech, and Octapharma and is the PI for the Wil-29/Wil-31 studies (Octapharma) and BAX-855 study and has served as a consultant for Bayer, Sigilon, Roche/Genentech, Octapharma, Grifols, Biomain, Sanofi, and Novo Nordisk. None of the other authors has any conflict of interest to declare.

## AUTHOR CONTRIBUTIONS

K.P.M. van Galen contributed to the concept and design, analysis, and/or interpretation of data and writing of drafts and final version of the paper. R. d'Oiron, P. James, R. Kadir, P. A. Kouides, R. Kulkarni, F. Peyvandi, and R. Winikoff contributed to concept and design, analysis and/or interpretation of data, critical writing and revising the intellectual content. J. N. Mahlangu, M. Othman, and D. Rotellini contributed to revising the intellectual content and approval of the manuscript to be published. R.F. Sidonio contributed to concept and design, analysis and/or interpretation of data, critical writing, and final approval of the version to be published.

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